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CVN Interview

FOCUSED UPDATE ON PCI FOR UNPROTECTED LEFT MAIN CAD

Long-Term Clinical Results Following Stenting of the Left Main Stem

Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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Objectives We investigated the long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease (ULMCA) patients treated by percutaneous coronary intervention with drug-eluting stent (DES).

Background There is limited information on long-term (>3 years) outcomes after DES implantation for ULMCA. Furthermore, bifurcation angle and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score are emerging as parameters for patient risk stratification, and their prognostic implications have still to be elucidated.

Methods One hundred forty-eight patients with ULMCA treated with DES were analyzed and compared with a historical cohort of 79 patients who received bare-metal stents for the treatment of ULMCA. Patient-oriented composite end point was defined as the occurrence of all-cause death, any myocardial infarction, or any revascularization.

Results The 4-year cumulative incidence of all-cause death, any myocardial infarction, any revascularization, and patient-oriented composite were 35.6%, 3.8%, 25.2%, and 54.4%, respectively. These end points had relatively increased from 1 year to 4 years by Δ70%, Δ5%, Δ50%, and Δ68%, respectively. When compared with a historical cohort who received bare-metal stents for ULMCA treatment, landmark analysis performed after the first 2 years of follow-up demonstrated that the DES cohort had significantly higher patient-oriented composite end point over the last 2 years of follow-up (26% vs. 8%, $p = 0.02$). EuroSCORE (European System for Cardiac Operative Risk Evaluation), cardiogenic shock, and SYNTAX score were identified as independent predictors for the 4-year patient-oriented composite, whereas bifurcation angle was not.

Conclusions Late increase in patient-oriented composite end points after DES implantation for ULMCA warrants careful and long-term follow-up. SYNTAX score and EuroSCORE appear to have a significant prognostic value in long-term patient risk. (J Am Coll Cardiol Intv 2010;3:584–94) © 2010 by the American College of Cardiology Foundation

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The prevalence of left main disease in patients with coronary artery atherosclerosis varies from 2.5% to 10% (1). Coronary artery bypass graft (CABG) remains the treatment of choice in patients with unprotected left main coronary artery disease (ULMCA) (2,3). Although percutaneous coronary intervention (PCI) using bare-metal stent (BMS) in patients having 2- or 3-vessel disease is associated with no significant difference in long-term mortality compared with CABG, restenosis and need for repeat revascularization remain major limitations of this mode of revascularization. These latter limitations have precluded the widespread use of PCI, not only in multivessel disease, but also in LM disease (4). Reduction of restenosis with drug-eluting stents (DES), however, has raised the possibility of their use for multivessel treatment as well as LM treatment. So far, several registries and randomized trials have investigated the short- and mid-term clinical outcomes of PCI using DES for ULMCA treatment (5–14), but little is known about its long-term safety and efficacy beyond 3 years (15). In addition, the rate of potentially fatal consequences of stent thrombosis or in-stent restenosis in this patient subset has not fully been investigated (16,17).

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Several clinical and angiographic parameters for risk stratification after PCI are emerging. Recently, EuroSCORE (European System for Cardiac Operative Risk Evaluation), a typically surgical risk stratification score, has been applied to the PCI population (18). As angiographic analysis, the angle between bifurcated branches has been recognized as a significant prognostic factor for immediate procedural outcomes as well as for intermediate-term outcomes (19–21). In addition, a comprehensive, angiographic scoring system, the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (22,23) based on morphology and location of coronary artery stenoses in the coronary tree has been proven to predict clinical outcomes in high-risk patients (9,24,25).

The main aim of this study was to report the long-term clinical outcomes of patients receiving DES for unprotected LM lesions in a daily practice of a tertiary medical center. In addition, we assessed the prognostic value of recently emerging predictors of adverse outcomes for PCI treatment of multivessel disease and ULMCA, such as EuroSCORE, the bifurcation angle, and SYNTAX score.

Methods

Study design and patient population. Between April 2002 and December 31, 2005, 210 consecutive patients underwent PCI for LM stenting (7,8). Sixty-two patients with a history of CABG were not retained in this analysis. The remaining 148 patients are the subject of the present investigation. On April 16, 2002, our institution adopted the use of sirolimus-eluting stents (Cypher, Cordis, Warren, New Jersey) as the default strategy for all coronary interventions, as part of RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry (26). On February 16, 2003, sirolimus-eluting stents were replaced by paclitaxel-eluting stents (Taxus Express2, Boston Scientific, Natick, Massachusetts) as the default stent, as part of the T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registry (27). For evaluation of long-term outcomes, this DES group was compared with a historical cohort who received BMS in the unprotected LM trunk before April 2002 (n = 79).

In this study, the decision to intervene in the patients with PCI was based on a consensus reached during a multidisciplinary medical surgical conference (the so-called heart-team conference) involving surgeon, interventionalist, and referring physician (28), except for patients who presented with ST-segment elevation myocardial infarction (STEMI), considering the emergent character of the clinical presentation. All procedures were performed according to standard clinical guidelines at the time. All patients were pretreated with 300 mg of clopidogrel. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for at least 3 months for patients with DES. Life-long aspirin therapy was recommended in all patients.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LM = left main
MACCE = major adverse cerebrovascular cardiac event
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery disease

QCA analysis. To assess the bifurcation angle between the left anterior descending and left circumflex arteries, 3-dimensional quantitative coronary angiography (QCA) analyses were performed by 2 observers blinded to the patient data and clinical outcomes. A validated program was used to reconstruct 3-dimensional images from 2 different projections at least 30° apart from each other (CardiOp-B system version 2.1.0.151, Paieon Medical Ltd., Park Afek, Israel) (29–31). Separate 3-dimensional angiographic images were constructed for systolic and diastolic phases. The bifurcation angle was defined as the angle between the left anterior descending and left circumflex arteries (32). In cases where the separate projections were not available, 2-dimensional bifurcation software (CAAS version 5.6, Pie Medical, Maastricht, the Netherlands) was used to calculate bifurcation angle (33). In primary PCI cases where TIMI (Thrombolysis In Myocardial

Infarction) flow grade was 0 or 1 pre-procedure, the cineangiography following the first balloon angioplasty was analyzed for the determination of the angle.

SYNTAX score. Two analysts blinded to patient characteristics and clinical outcomes reviewed the angiograms to calculate the SYNTAX score (22,23). In case of disagreement, the opinion of a third observer was obtained and the final decision was made by consensus. Each coronary lesion producing >50% luminal obstruction in vessels >1.5 mm was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the following: 1) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (34); and 2) the morphologic features of each single lesion (35,36). The reproducibility of the SYNTAX score was recently reported (22).

Clinical follow-up. Survival data for all patients were obtained from municipal civil registries on a yearly basis. A questionnaire was subsequently sent to all living patients with specific enquiries on rehospitalization and major adverse cardiac events (MACE). As the principal regional cardiac referral center, most repeat revascularization (either percutaneous or surgical) is normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary. Causes of death were obtained from medical records when they happened during hospitalization, and otherwise from the Central Bureau of Statistics, The Hague, the Netherlands (37,38). Causes of death were classified according to the International Classification of Diseases and Related Health Problems-10th Revision. For the present analysis, death from ischemic heart disease (I-20 to I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasm (C-009 to C-97). All the remaining deaths were classified as being due to other causes, and no further distinction was made. In this study, there was no mandatory angiographic follow-up.

End point definitions. The primary end point was a patient-oriented composite defined as all-cause death or any myocardial infarction (MI) or any revascularization (all surgical and percutaneous, target lesion, target vessel, and non–target vessel revascularization) according to the Academic Research Consortium definitions (39). The secondary end point was the device-oriented composite end point defined as cardiac death, MI in the target vessel territory, or a target lesion revascularization. In addition, each individual component end point was analyzed in a nonhierarchical way. Definite stent thrombosis was also considered as a separate secondary end point.

Myocardial infarction included periprocedural MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3 times the upper limit of normal), reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values), or spontaneous MI (diagnosed by any rise in creatine kinase-myocardial band fraction above the upper limit of normal) (40). Target lesion revascularization was defined as a repeat revascularization of in-stent or within 5 mm proximal or distal to the stent implanted in the index procedure (41). Target vessel revascularization (TVR) was defined as any revascularization in the same epicardial vessel treated in the index procedure. Definite stent thrombosis was defined as TIMI flow grade 0 or 1 or the presence of a flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention (42). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year), or very late (more than 1 year) (39).

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent *t* test for continuous variables and Pearson chi-square test for categorical variables. All statistical tests were 2-tailed, and p value of <0.05 was considered as statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the current cohort and the historical control. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression models were built to elucidate independent predictors of clinical end points. Significant variables in univariate analysis ($p < 0.1$) were selected to put in the multivariate model. The following pre-procedural variables were included in the initial univariate analysis: gender, diabetes, current smoking habit, hypertension, hypercholesterolemia, age, previous history of myocardial infarction or PCI, SYNTAX score, EuroSCORE, shock at entry, clinical presentation, and bifurcation angle. Clinical presentation (STEMI, unstable angina or non-STEMI, and stable angina) was coded as a categorical variable. Bifurcation angle was partitioned according to tertiles (lowest tertile as a reference). The results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed with SPSS version 16 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics. The baseline and procedural characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
Demographics			
Age, yrs	64.9 ± 12.1	65.1 ± 11.2	0.96
Men	108 (73)	49 (62)	0.10
Diabetes	24 (16.2)	15 (19)	0.59
Hypertension	61 (41)	34 (43)	0.89
Hypercholesterolemia	80 (54)	34 (43)	0.13
Family history of coronary artery disease	47 (32)	15 (19)	0.04
Current smoking	27 (18)	14 (18)	1.00
Previous PCI	32 (22)	25 (32)	0.11
Previous MI	49 (33)	24 (30)	0.77
Additive EuroSCORE	4.26 ± 3.54	4.37 ± 3.57	0.82
SYNTAX score	39.4 ± 22.9	36.8 ± 24.6	0.96
LVEF, %	45.3 ± 13.6	41.8 ± 16.9	0.48
Presentation			
STEMI	36 (24.3)	22 (27.8)	0.64
Stable angina	60 (40.5)	30 (33.3)	0.78
Unstable angina/non-STEMI	52 (35.1)	27 (34.2)	1.00
Shock at entry	13 (8.8)	6 (7.6)	1.00
Pre-procedural quantitative angiographic analysis			
Bifurcation angle in diastole, °	94.1 ± 25.5	89.5 ± 25.3	0.29
Bifurcation angle in systole, °	84.9 ± 26.6	81.42 ± 23.8	0.42
Minimal lumen diameter, mm	1.09 ± 0.32	1.08 ± 0.27	0.92
Reference vessel diameter, mm	3.35 ± 2.49	3.31 ± 0.36	0.69
Procedural characteristics			
Number of implanted stents	3.08 ± 0.37	2.85 ± 0.47	<0.0001
Total stented length per patient	59.9 ± 40.4	42.4 ± 28.4	<0.0001
Average stent diameter	3.08 ± 0.37	3.52 ± 0.47	<0.0001
Clopidogrel duration in month	7.53 ± 5.32	5.27 ± 4.86	0.01
IVUS use	48 (32)	34 (43)	0.15
Stenting strategy			
Provisional	114 (77)	70 (89)	0.07
Culotte	13 (9)	1 (1)	
T-stenting	15 (10)	8 (10)	
Crush stenting	4 (3)	0	
Kissing technique	2 (1)	0	
Post-procedural bifurcation angle			
Bifurcation angle in diastole, °	85.1 ± 24.8	84.2 ± 25.9	0.83
Bifurcation angle in systole, °	80.0 ± 23.7	76.7 ± 21.2	0.38

Values are expressed as n (%) or mean ± SD.

BMS = bare-metal stents; DES = drug-eluting stents; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

The mean age of the patients was 64.9 years old, 16.2% of the patients had diabetes, and 33% had previous history of MI. Approximately one-quarter of patients presented with STEMI, and 8% presented with severe hemodynamic compromise at entry. The average additive EuroSCORE and SYNTAX score was 4.26 and 39.4, respectively.

Clinical outcomes. Clinical follow-up was available in all patients, with a median duration of follow-up of 1,473 days (interquartile range: 1,182 to 1,848 days) for patients alive at follow-up. Hierarchical count of adverse events is shown in Table 2. Patient-oriented composite increases from 32.4% at 1 year to 51.4% at 4 years (Δ58%), which was mainly driven by an increase in all-cause mortality from 19.6% at 1 year to 33.1% at 4 years, a relative increase of 68%. There was 1 case of definite late stent thrombosis at 1 year, and there was 1 case of definite very late stent thrombosis at 4 years.

Kaplan-Meier estimates of clinical end points are presented in Figures 1A to 1C. At 4 years, the cumulative

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Table 2. Hierarchical Count of Patient-Oriented Composite After DES Implantation Compared With the Historical Cohort With BMS

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
1 yr			
All-cause death	29 (19.6)	23 (29.1)	0.14
Any MI	2 (1.4)	1 (1.3)	1.00
Any revascularization	17 (11.5)	10 (12.7)	1.00
Patient-oriented composite	48 (32.4)	34 (43)	0.15
2 yrs			
All-cause death	35 (23.6)	27 (34.2)	0.11
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	19 (12.8)	11 (13.9)	0.84
Patient-oriented composite	57 (38.5)	39 (49.4)	0.12
3 yrs			
All-cause death	41 (27.7)	29 (36.7)	0.18
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	23 (15.5)	11 (13.9)	0.85
Patient-oriented composite	67 (45.3)	41 (51.9)	0.4
4 yrs			
All-cause death	49 (33.1)	30 (38)	0.47
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	24 (16.2)	11 (13.9)	0.7
Patient-oriented composite	76 (51.4)	42 (53.2)	0.9

Event rates were calculated as number of events divided by total number of patients and therefore differ from those in the figures, where event rates were calculated by Kaplan-Meier methods. In this table, comparison was made with the chi-square or Fisher exact test.

Abbreviations as in Table 1.

incidence of all-cause death, MI, any revascularization, and patient-oriented composite were 35.6% (95% CI: 27.3% to 43.8%), 3.8% (95% CI: 0.5% to 7.1%), 25.2% (95% CI: 16.9% to 33.6%), and 54.4% (95% CI: 45.8% to 63.1%), respectively. Cardiac mortality, all-cause mortality, and any revascularization rate relatively increased from 1 year to 4 years by Δ68%, Δ82%, and Δ49%, respectively, whereas the changes in target lesion revascularization and MI was less increased from 1 year to 4 years (Δ5% and Δ28%, respectively) (Figs. 1A and 1B). In summary, the device-oriented and patient-oriented composite increased from 1 year to 4 years by Δ56% and Δ68%, respectively (Fig. 1C). If stratified by the presentation with STEMI versus others (non-STEMI, unstable angina, and stable angina), the patient-oriented composite was higher in STEMI patients (68.6%) than the others (49%, $p < 0.001$), also the device-oriented composite, all-cause death, and cardiac death were higher in the STEMI patients than the others (53% vs. 30%, $p < 0001$; 55% vs. 29%, $p < 0.001$; 48% vs. 16%, $p < 0.001$) (Fig. 2A). With stratification according to the tertiles of EuroSCORE (<2, ≥2 and <5, ≥5), the patient-oriented composite was higher in the high tertile (76.8%) than in the low (41.2%, log-rank $p < 0.001$) or intermediate tertiles (51.8%, log-rank $p < 0.001$) (Fig. 2B). If stratified according to type of DES (Cypher and Taxus), the patient-oriented composite was

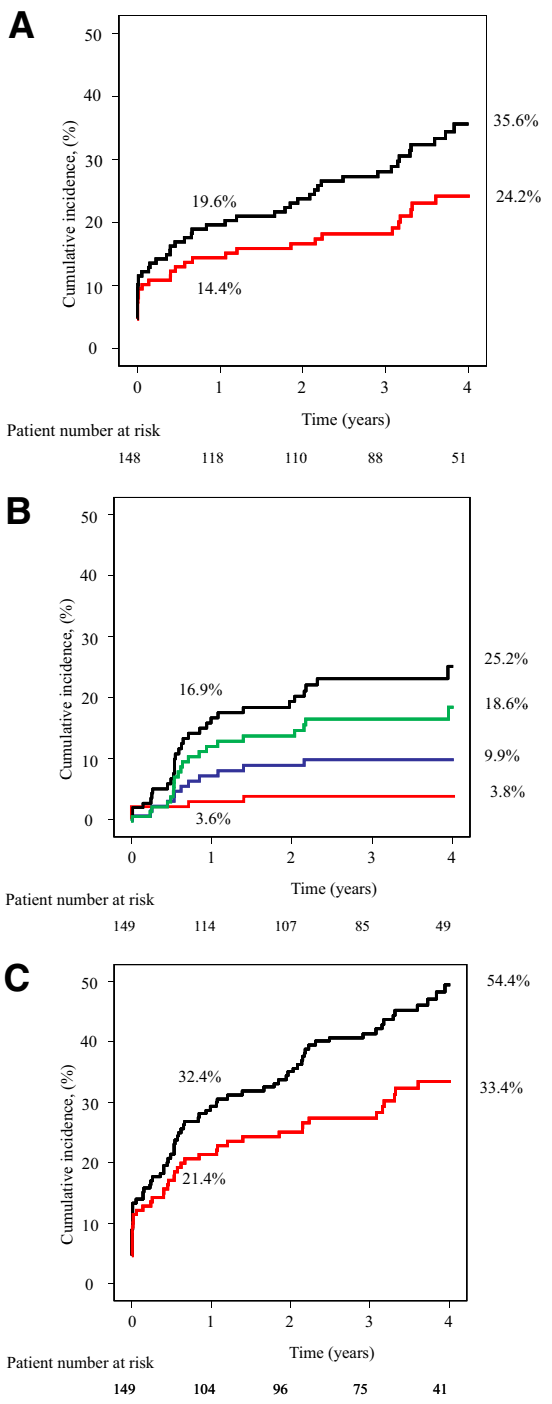

Figure 1. Kaplan-Meier Estimates After Implantation of DES

(A) Kaplan-Meier estimates demonstrate all-cause mortality **(black line)** and cardiac mortality **(red line)**. **(B)** Kaplan-Meier estimates present the end points of any myocardial infarction **(red line)**, target lesion revascularization **(blue line)**, target vessel revascularization **(green)**, and any revascularization including target and non–target vessel revascularization **(black line)**. **(C)** Kaplan-Meier estimates show the composite end point **(red line)** of cardiac mortality, myocardial infarction in the stented vessel territory, or target lesion revascularization and the composite end point **(black line)** of all-cause mortality, any myocardial infarction, or any revascularization. DES = drug-eluting stent.

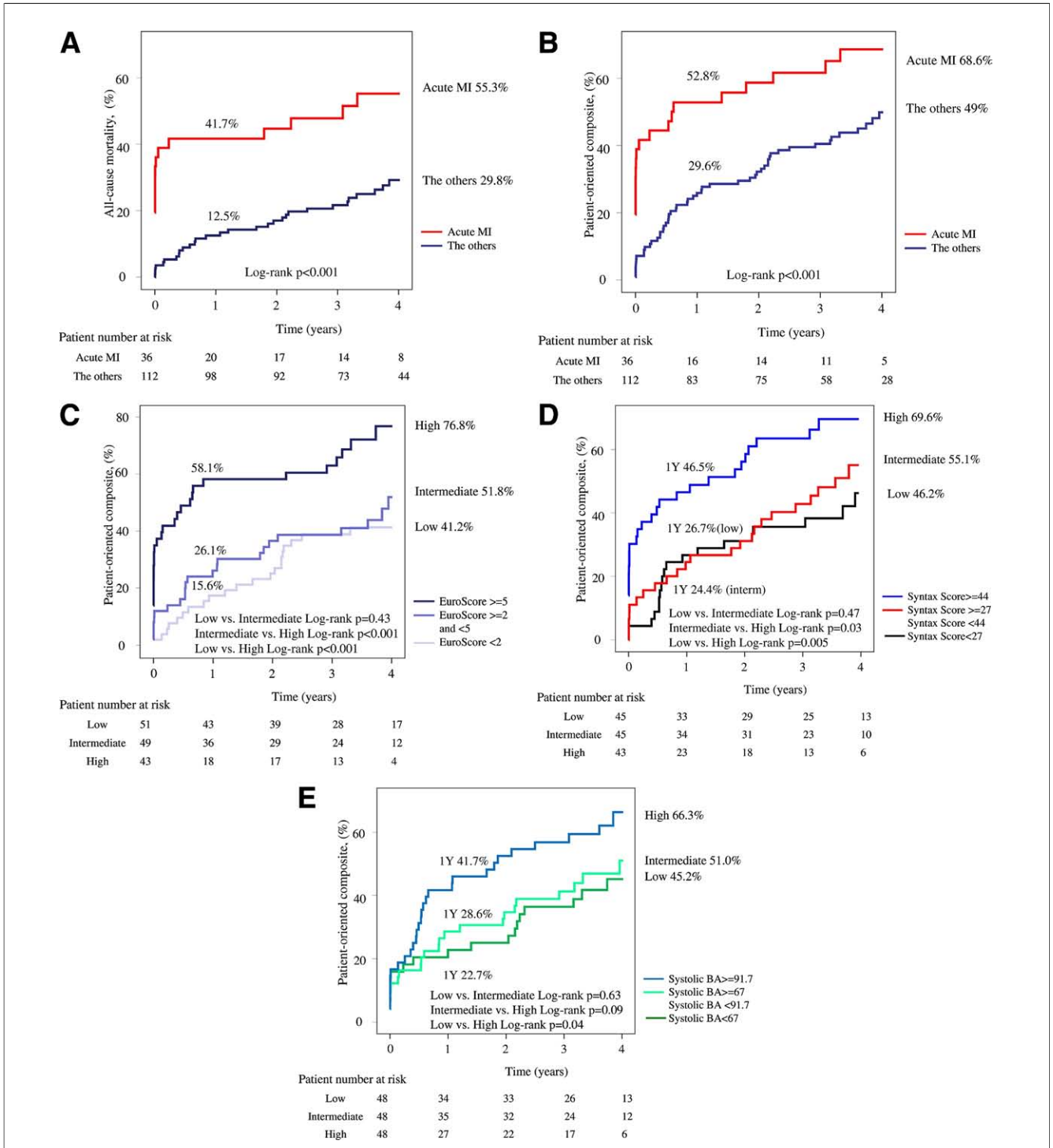

Figure 2. Kaplan-Meier Estimates After Implantation of DES With Stratification of Subgroups

(A) All-cause mortality and **(B)** patient-oriented composite end point (all-cause mortality, any myocardial infarction [MI]), or any revascularization) according to a presentation of ST-segment elevation myocardial infarction or the others (stable angina, non–ST-segment elevation myocardial infarction, or unstable angina). Patient-oriented composite end point stratified by **(C)** tertile division of EuroSCORE (European System for Cardiac Operative Risk Evaluation) with cutoff values of 2 and 5 and **(D)** tertiles of SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score of the current cohort (cutoff values of 27 and 44). **(E)** The patient-oriented composite end points were classified according to tertiles of bifurcation angle (BA) between the left anterior descending and circumflex arteries (cutoff values of 67 and 91.7). Abbreviations as in Figure 1.

53.8% in Cypher and 54.8% in paclitaxel-eluting stent (p = 0.83), whereas the all-cause mortality was 30.8% versus 36.5%, respectively (p = 0.56).

Comparison with historical cohort. Patient demographics in the historical control (n = 79) were similar to the current cohort except for a lower frequency of family history of coronary artery disease (32% vs. 19%, p = 0.04), reflecting that the changes in clinical practice, number of implanted stents, stent length, stent diameter, and clopidogrel duration are higher in the current cohort than in the historical control group.

Figure 3 shows the Kaplan-Meier estimates of all-cause mortality and the patient-oriented composite end point of the current cohort with DES and the historical control with BMS. At 1 year, the rate of all-cause death (current cohort 19.6% vs. historical cohort 29.1%) and patient-oriented composite (32.4% vs. 43.0%) was lower in the current cohort than in the historical cohort (Figs. 3A and 3B). At 4 years the events rate, however, became comparable between the 2 groups (all-cause mortality: 38.0 vs. 35.6%, p = 0.48; patient-oriented composite: 54.4 vs. 53.2%, p = 0.64) as a result from a late increase of events in the current cohort. Kaplan-Meier estimate before 2 years yielded a numerically higher patient-oriented composite end point in the historical cohort (log-rank p = 0.1), whereas landmark analysis (Fig. 3B) after the second year demonstrated a significantly higher event rate in the current cohort than the historical cohort (log-rank p = 0.02).

SYNTAX score. In the current cohort, the SYNTAX score ranged from 7 to 104 with median of 33.0. If the SYNTAX score is divided into tertiles, the cutoff values were 27.0 and 44.0. The Kaplan-Meier curves of device-oriented composite stratified by these tertiles of SYNTAX score are presented in Figure 2C. The 4-year event rates were 46.2%, 55.1%, and 69.6% in low, intermediate, and high tertile groups, respectively. High tertile group demonstrated significantly higher event rates than intermediate tertile (log-rank p = 0.03) and low tertile (log-rank p = 0.005) groups did.

Three-dimensional QCA analysis. Three-dimensional QCA analysis was feasible in only 50.7% of patients due to the unavailability of 2 separate angiographic views of more than 30° that is a prerequisite for 3-dimensional QCA; in the remaining patients, 2-dimensional QCA was performed. The results are shown in Table 1. In the patient receiving DES, the Kaplan-Meier curves of patient-oriented composite were separated according to the tertiles of systolic bifurcation angle (high >91.7, intermediate ≤91.7 and >67, low ≤67) as shown in Figure 2E. High tertile group demonstrated higher patient-oriented composite at 4 years (66.3%) than the intermediate (51.0%) and the low (45.2%) groups did (log-rank high vs. low: p = 0.04; high vs. intermediate: p = 0.09).

Predictor of adverse events. Table 3 shows the results of the univariate and multivariate analyses to identify the predictors for all-cause mortality and for patient-oriented composite. Bifurcation angle did not remain as a significant predictor of either all-cause mortality or patient-oriented end point in the multivariate analysis.

At 1 year, multivariate analysis demonstrated that EuroSCORE, age, shock at entry, and SYNTAX score were independent predictors for all-cause mortality and patient-

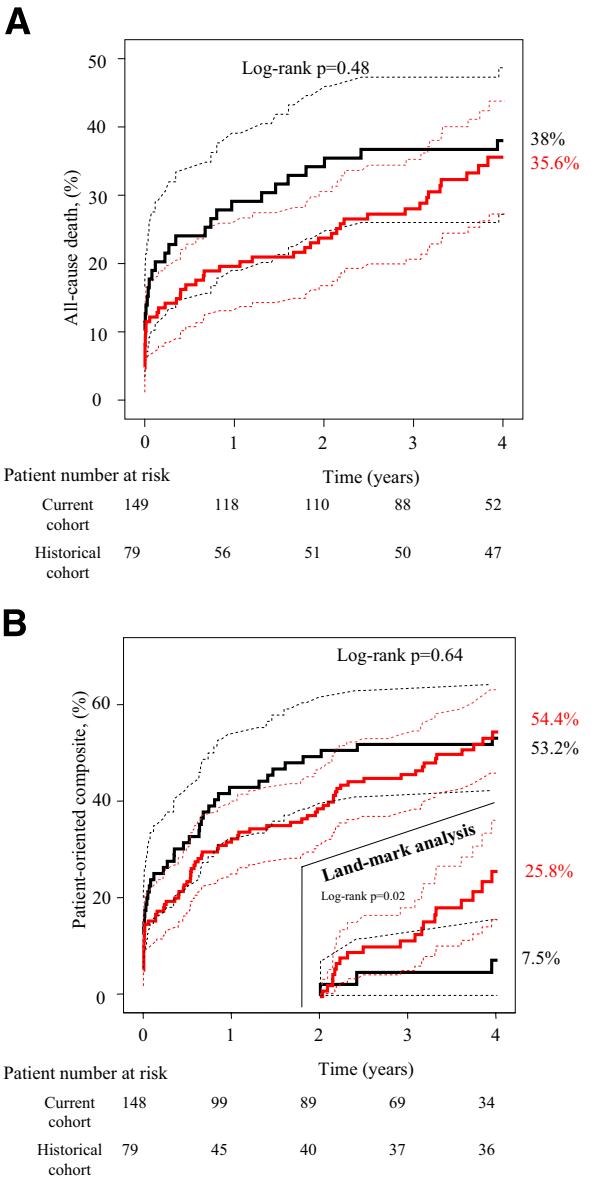

Figure 3. Kaplan-Meier Estimates of DES and BMS Cohorts

Kaplan-Meier estimates of the current cohort treated with drug-eluting stent **(red line)** or historical cohort treated with bare-metal stent **(black line).** All-cause mortality is demonstrated in **(A)**, whereas **(B)** demonstrates patient-oriented composite end point (all-cause mortality, any myocardial infarction, or any revascularization) with a landmark analysis more than 2 years after implantation. **Dotted lines** = 95% confidence interval. BMS = bare-metal stent(s); other abbreviations as in Figure 1.

Table 3. Univariate and Multivariate Analysis for Predictors of All-Cause Mortality and Patient-Oriented Composite After DES Implantation in the Left Main Trunk

	All-Cause Mortality				Patient-Oriented Composite			
	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value
1-year outcome								
EuroSCORE	1.26 (1.17–1.36)	<0.001	1.24 (1.11–1.39)	<0.001	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009
Presentation of STEMI*	6.77 (3.56–18.66)	<0.001			4.38 (2.08–9.23)	<0.001		
Age	1.06 (1.02–1.09)	0.003	1.05 (1.01–1.10)	0.03	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009
Shock at entry	8.56 (3.83–19.1)	<0.001	4.21 (1.50–1.82)	0.006	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001
SYNTAX score†	1.35 (1.17–1.56)	<0.001	1.23 (1.06–1.42)	0.006	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03
Hypercholesterolemia	0.33 (0.15–0.73)	0.006			0.43 (0.24–0.76)	0.004		
Hypertension	0.41 (0.18–0.96)	0.04	0.34 (0.13–0.88)	0.03	0.45 (0.24–0.84)	0.01		
4-year outcome								
EuroSCORE	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009	1.16 (1.09–1.24)	<0.001	1.09 (1.02–1.16)	0.02
Presentation of STEMI*	4.38 (2.08–9.23)	<0.001			3.42 (1.69–6.94)	0.001		
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009	1.04 (1.01–1.070)	0.004		
Shock at entry	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001	4.61 (2.21–6.61)	<0.001	2.74 (1.30–5.80)	0.008
SYNTAX score†	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03	1.22 (1.08–1.38)	0.001	1.12 (1.01–1.24)	0.4
High bifurcation angle‡					1.99 (0.93–4.26)	0.075		

Univariate or multivariate hazard ratios were calculated by Cox regression models.
*Stable angina used as a reference. †Each 10-point increase of SYNTAX score. ‡Low tertile bifurcation angle used as a reference.
Abbreviations as in Table 1.

oriented composite. At 4 years, in the final multivariate models, age, shock at entry, the SYNTAX score and EuroSCORE remained as independent predictors for all-cause mortality, whereas EuroSCORE, shock at entry, and SYNTAX score were identified as independent predictors for patient-oriented composite.

Discussion

The main findings of the current study are the following: 1) At 4-year follow-up after DES implantation in ULMCA, patient-oriented composite end point was 51.4% with a 58% relative increase of events from 1 year to 4 years. 2) A landmark analysis of the last 2 years of follow-up indicated a higher composite end point for the current cohort with DES when compared with the historical cohort with BMS (25% vs. 8%, p = 0.02). 3) EuroSCORE and SYNTAX score were independent predictors for both all-cause mortality and the patient-oriented composite end point up to 4 years, whereas pre-procedural bifurcation angle between the left circumflex and left anterior descending arteries was not.

According to the current guidelines of the European Society of Cardiology and the American Heart Association and American College of Cardiology guidelines (40,43), the presence of a stenosis in the LMCA is a class IIB or III indication for PCI unless the patient is not eligible for CABG in presence of extreme comorbidities and STEMI. In the recent U.S. criteria for appropriateness of revascularization, percutaneous treatment of LM disease is considered "inappropriate" (2). In European daily practice, however, 4.6% of patients treated in the catheterization lab have LM stenosis, and 58% of those are treated by percutaneous means (44).

Up to now, 2 randomized trials have been performed to compare CABG and PCI using DES in patients undergoing treatment for LM disease. In the LE MANS (Left Main Coronary Artery Stenting) study by Buszman et al. (10), PCI was associated with a lower 30-day risk of major adverse cerebrovascular cardiac event (MACCE) (p = 0.03) and had comparable 1-year mortality or MACCE to surgery. In the more recent SYNTAX trial (9), which randomized 1,800 patients with 3-vessel or LM coronary artery disease to either CABG or PCI, the use of PCI at 1 year was associated with safety end points (death, cerebrovascular accident, and MI) but a higher rate of MACCE than CABG, due to a significantly higher rate of revascularization. However, in the subgroup of patients with LM disease with an average SYNTAX score of 28.1, PCI and CABG were associated with similar MACCE rates at 1 year (PCI 15.8% vs. CABG 13.6%). In the DES cohort of the present study, the 1-year all-cause mortality and revascularization rate of patients treated with DES (19.6% and 16.9%, respectively) were higher than rates reported in the LM subgroup of the randomized cohort in the SYNTAX trial (4.2% and 12.0%, respectively). This is likely due to the high-risk nature of our all-comers registry (e.g., including 24% STEMI patients with a mean EuroSCORE of 4.26 and an average SYNTAX score of 39.4).

In this analysis, we selected a patient-oriented composite end point as a primary end point, because it represents the most critical clinical approach for a population undergoing a new form of treatment. The Academic Research Consortium defined 2 methodological approaches to report clinical follow-up: 1) the device-oriented composite end point; and 2) the patient-oriented composite end point. The device-oriented approach put the accent on the efficiency and efficacy of a new device, therefore, focusing on the cardiac death, MI, and reintervention related to the device. The patient-oriented end point is a follow-up, which specifically considers the welfare of the patient, and includes all-cause death, any MI, and any revascularization.

In the current analysis, we entered only the pre-procedural parameters in the multivariate analysis and excluded the procedural variables such as angulation after stenting, technique of stenting, number of stent, length of stent, and so forth, because they are factors reflecting the treatment modalities rather than the anticipated prognosis of the treatment. Parameters describing lesion characteristics were also excluded because they were incorporated in the SYNTAX score: for example, Medina classification, chronic total occlusion, American College of Cardiology/American Heart Association lesion classification (45).

Long-term outcomes after PCI in the LM population are limited. Park et al. (46) reported the 3-year safety composite rate (death, Q-wave MI, or stroke) of 9.7% with TVR rate of 12.6%. Vaquerizo et al. (12) demonstrated the device-oriented composite end point at 2 years of 12.6% after UCLMA stenting with paclitaxel-eluting stents in 291 patients from multicenter registry. In these registries, the patients with acute MI or cardiogenic shock were excluded; whereas in our registry, such patients were included and had a negative impact on clinical outcomes. Also, frequent use of intravascular ultrasound might contribute the relatively lower mortality in the Korean registry than in our European registry (46). In one of largest "all-comer" DELFT (Drug-Eluting Stent for Left Main) registries exclusively using DES in ULMCA with 3-year complete follow-up, Meliga et al. (15) demonstrated 3-year MACE rate (a composite of cardiac mortality, MI, and TVR) of 26.5%, cardiac mortality of 9.2%, and TVR of 14.2%. If the same composite definition were applied to the present study, the 3-year MACE rate in our study (26.0%) would be similar to the DELFT registry (26.5%). Wood et al. (47) reported a long-term outcome of 100 patients with high surgical risk after PCI. All-cause mortality at 28 months was 21%; event-free survival was around 65% at 27 months (47).

In the current study, the baseline patient demographics are comparable between the current and the historical cohorts. Although the anatomical complexity reflected by SYNTAX score was comparable between the 2 cohorts (the current cohort 39.4 vs. the historical control 36.8, $p = 0.96$), the cohort with DES was more aggressively treated than the historical cohort with BMS, as indicated by a higher incidence of bifurcation stenting (48% vs. 57%, $p = 0.04$), by a larger number of stents implanted (2.85 ± 0.47 vs. 3.08 ± 0.37), and by on average a longer stented length (42.4 ± 28.4 mm vs. 59.9 ± 40.4 mm).

The source of our concerns is the increase of the patient-oriented composite in the DES group between 2 and 4 years, which was significantly higher than in the historical cohort of BMS, and the long-term safety of DES in the treatment of patients with ULMCA remains an unanswered question. One possible explanation for unfavorable follow-up could be the occurrence of occult stent thrombosis. Occlusion of the LM trunk with thrombus is likely to be lethal. Thus, patients can present with sudden and/or out-of-hospital death rather than with angiographically proven stent thrombosis. The very late stent thrombosis presenting with out-of-hospital death, however, can be undiagnosed and under-reported. The cause of death was obtained from the civil registry, and it is up to the general practitioners to classify the cause of mortality according to International Classification of Diseases and Related Health Problems-10th Revision unless the patient passed away in the hospital. Therefore, no attempt was made to impute death to possible or probable stent thrombosis.

In the large multicenter registry ($n = 731$) by Chieffo et al. (17), the cumulative incidence of stent thrombosis at 29.5 months after LM stenting was reported to be 0.95% for definite stent thrombosis and 2.7% for possible stent thrombosis. In DELFT registry (15) ($n = 358$) at ≥3-year follow-up, the incidence of definite, probable, and possible stent thrombosis were 0.6%, 1.1%, and 4.4%. In ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) trial (48) ($n = 607$), the 2-year rate of definite or probable stent thrombosis was about 0.5% to 1.0%. In a series of high surgical risk patients, Wood et al. (47) reported a 5% possible stent thrombosis presenting as sudden death. Taking into account the late increase in mortality shown in our study, follow-up extending beyond 3 years is warranted for patients receiving DES in the setting of ULMCA.

The bifurcation angle has been shown to relate not only to the difficulty level of the procedure but is also associated with intermediate outcomes. Dzavik et al. (19) reported that a bifurcation angle ≥50 was an independent predictor of MACE at 1 year after bifurcation crush stenting in 133 patients. In 132 patients receiving Cypher stents in bifurcations excluding LM lesions, Adriaenssens et al. (49) reported that increasing bifurcation angles is an independent predictor of binary restenosis (HR: 1.53 [95% CI: 1.04 to 2.23] per 10° increase in angulation) after culotte stenting. The worse outcomes in high-angulated bifurcation lesions might be the result of the adjacent presence of low and high shear stress found in bifurcation lesions. High

shear stress possibly stimulates platelet activation and aggregation, and low shear stress might enhance deposition of platelets. This mechanism can be potentially exaggerated in higher bifurcation angles. Furthermore, when bifurcation stenting is performed in high-angle lesions, the stent will likely not appose against the wall of bifurcation (50), especially in the ostium of the left circumflex artery (20). In the present study, however, we observed that the bifurcation angle between the left anterior descending and left circumflex arteries was not an independent predictor for adverse events, although there is a weak statistical association with 4-year composite end points in the univariate analysis (HR: 1.99 [95% CI: 0.93 to 4.26], p = 0.07).

Study limitations. This study has several limitations. This is a single center, observational study that included a modest number of patients. The results of this landmark analysis (reporting a higher event rate in patients treated with DES compared with BMS after 2 years) would need to be confirmed in a larger study. In addition, the low 1-year mortality rate compelled us to include only 2 or 3 independent variables in the Cox regression model, resulting in overfitting of the model. Confounding factors, such as procedural variables, might have been overlooked. Although baseline characteristics were similar in the historical BMS and current DES groups, some procedural variables were in fact different and as a result might have influenced outcomes.

Conclusions

Our study reports a late increase in adverse events up to 4 years, which warrants careful follow-up of the patient receiving DES in the LM trunk. The SYNTAX score and EuroSCORE can be considered important components of risk stratification.

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